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Left lateral parietal rTMS improves cognition and modulates resting brain connectivity in patients with Alzheimer's disease: Possible role of BDNF and oxidative stress

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ABSTRACT

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive neuromodulation technique which is increasingly used for cognitive impairment in Alzheimer's Disease (AD). Although rTMS has been shown to modify Brain-Derived Neurotrophic Factor (BDNF) and oxidative stress levels in many neurological and psychiatric diseases, there is still no study evaluating the relationship between memory performance, BDNF, oxidative stress, and resting brain connectivity following rTMS in Alzheimer's patients. Furthermore, there are increasing clinical data showing that the stimulation of strategic brain regions may lead to more robust improvements in memory functions compared to conventional rTMS. In this study, we aimed to evaluate the possible disease-modifying effects of rTMS on the lateral parietal cortex in AD patients who have the highest connectivity with the hippocampus. To fill the mentioned research gaps, we have evaluated the relationships between resting-state Functional Magnetic Resonance Imaging (fMRI), cognitive scores, blood BDNF levels, and total oxidative/antioxidant status to explain the therapeutic and potential disease-modifying effects of rTMS which has been applied at 20 Hz frequencies for two weeks. Our results showed significantly increased visual recognition memory functions and clock drawing test scores which were associated with elevated peripheral BDNF levels, and decreased oxidant status after two weeks of left lateral parietal TMS stimulation. Clinically our findings suggest that the left parietal region targeted rTMS application leads to significant improvement in familiarity-based cognition associated with the network connections between the left parietal region and the hippocampus.

1. Introduction

Alzheimer's Disease (AD) is the most common type of dementia and is characterized by the gradually progressive neurodegenerative process, which typically begins with memory impairment (Ergis & Eusop-Roussel, 2008; Fleischman et al., 2005; Gold & Budson, 2008; Kidd, 2008). Current treatment modalities failed to alter the neurodegenerative course, and almost all phase III clinical trials have been unable to reach the primary endpoint (Mehta et al., 2017). These findings together underline the importance of expanding the horizon beyond the biomarker, amyloid, and tau hypotheses when searching for novel treatment strategies of AD. Repetitive Transcranial Magnetic

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Stimulation (rTMS) is a technique which permits non-invasive modulation of the cortical activity (Klomjai, Katz, & Lackmy-Vallée, 2015). Due to its tolerable side effect profile, TMS is increasingly used in the treatment of major depression and cognitive symptoms in neurodegenerative dementias (Elder & Taylor, 2014; Janicak & Dokucu, 2015; Ni & Chen, 2015). Relatedly, there are pieces of evidence suggesting its potential therapeutic role for cognitive impairment in AD (Chou, That, & Sundman, 2019; Gonsalvez, Baror, Fried, Santarnecchi, & Pascual-Leone, 2016; Nardone et al., 2014). For instance, the latest meta-analysis covering 13 studies has suggested that modifying the dorsolateral prefrontal cortex (DLPFC) and right frontal gyrus might have significant beneficial effects on cognitive and executive functions which lasted between 4 weeks to 12 weeks (Chou et al., 2019). Although it is not possible to directly stimulate the deeply located hippocampus with TMS, studies have recently revealed that the stimulation of specific superficial brain regions that are highly connected with the hippocampus might indirectly alter hippocampal activity. It has been already demonstrated that the left parietal cortex along with its subregions such as intraparietal sulcus, angular gyrus, supramarginal gyrus, and inferior parietal lobule (Guidali, Pisoni, Bolognini, & Papagno, 2019; Nelson et al., 2010; Rugg & King, 2017; Sestieri, Shulman, & Corbetta, 2017; Wang et al., 2019), and its connectivity with the hippocampus, are involved in different degrees of memory function. For instance, several studies have shown the formation of episodic and autobiographical memory retrieval (Hutchinson, Uncapher, & Wagner, 2009; King, Chastelaine, Elward, Wang, & Rugg, 2015; Robin et al., 2015; Wagner, Shannon, Kahn, & Buckner, 2005) may involve also a recognition process such as familiarity and recollection (Rugg & King, 2017; Vilberg & Rugg, 2009; Wagner et al., 2005). For instance, Warren et al. have recently demonstrated that left parietal cortex stimulation led to a significant functional magnetic resonance imaging (fMRI) activity compared to the stimulation of the prefrontal cortex during the autobiographical memory formation (Warren, Hermiller, Nilakantan, & Voss, 2019). In line with this, numerous studies have shown that the connectivity of the parietal memory network including the inferior parietal lobule is disrupted in AD (Greene & Killiany, 2010; Hu et al., 2019).

In a similar vein, lateral parietal cortex stimulation resulted in significant cognitive improvement compared to conventional rTMS application strategies (Nilakantan et al., 2017; 2019;; Wang et al., 2014; Wang & Voss, 2015). Furthermore, resting-state fMRI has a crucial role in uncovering local network connectivity disruptions (de Ridder, Klein, & Kim, 2018). In accord with this, recent evidence suggests that functional brain changes precede structural brain changes in AD (Burggren & Brown, 2014). Given this, it is not unreasonable to assume that fMRI combined with clinically relevant disease progression parameters (i.e., Brain-Derived Neurotrophic Factor (BDNF), oxidative stress) could be highly sensitive in detecting functional, neurometabolic, and neurochemical brain changes related to AD pathology. Interestingly, although less studied, some recent evidence suggests that rTMS may also have a disease-modifying effect in AD patients besides its well-known beneficial effects on cognition (Gonsalvez et al., 2016; Nardone et al., 2014; Rajji, 2019).

Considering all of these findings, resting-state fMRI combined with blood serum levels such as BDNF and oxidative stress could be considered promising biomarkers for AD in predicting therapeutic response to the modulation of the disrupted functional network. For instance, a recent meta-analysis (Vemuri, Jones, & Jack, 2012) has shown that the most consistent finding across previous resting-state fMRI studies of AD was impaired functional connectivity in the posterior default mode network (i.e., precuneus and posterior cingulate cortex) (Damoiseaux, 2012; Klaassens et al., 2017). However, although rTMS has been shown to modify BDNF and oxidative stress levels in stroke (Niimi et al., 2016) and depression patients (Zhao et al., 2019), we could not find any study on the effects of TMS on BDNF and oxidative and antioxidative parameters in Alzheimer's patients in the literature (Durmaz et al., 2018). Several studies have revealed that BDNF synthesis and secretion are disrupted in different stages of AD progression which are associated with abnormal amyloid-beta (Aβ) accumulation, synaptic impairment, and cognitive dysfunction (Borba et al., 2016; Song, Yu, & Tan, 2015). Further studies have indicated that oxidative stress is strongly linked with BDNF dysfunction (Archer, 2017; Kapczinski et al., 2008; Molinari et al., 2020) by creating an impaired vicious cycle of Aβ and tau protein accumulation and mitochondrial dysfunction (Chauhan & Chauhan, 2006; Chen & Zhong, 2014). These findings align with the human data showing that BDNF and oxidative stress levels are important parameters for AD outcome (Horvat et al., 2016).

In the light of rapidly replicating evidence regarding the therapeutic correlates of the clinical pro-cognitive effects of rTMS (Hallett, 2007; Kobayashi & Pascual-Leone, 2003), our rationale for applying such a wide range of correlation analyses was to examine the relationship among the BDNF serum levels, oxidant and antioxidant parameters, and the neuropsychometric test scores after the rTMS application.

In this study, we aimed to evaluate the possible disease-modifying effects of rTMS on the lateral parietal cortex in AD patients with the highest connectivity with the hippocampus. In this context, we have combined fMRI measurements, cognitive data, and blood levels of BDNF and oxidant status to explain the therapeutic and potential disease-modifying effects of rTMS applied at 20 Hz frequencies for two weeks.

2. Methods

2.1. Subjects

G*power (ver. 3.1.6.6) software was used to determine the sample size. We have found that at least the sample size of $n = 13$ subjects are required for 90% power with a significance level of $\alpha = 0.05$ which led us to include at least $n = 15$ subjects in the study. Nineteen Alzheimer patients were included in our study (12 females, ages 56–84 years). Incomplete datasets were collected from four patients, of whom two were not suitable for MRI, one had a flu infection and one was seriously injured before the evaluation. Finally, these datasets were excluded from analyses according to the exclusion criteria (Greene, Black, & Schlaggar, 2016; Rossi et al., 2009). We concluded our study with 15 Alzheimer's patients. All patients were eligible for MRI and TMS procedures on standard MRI safety screening as well as on their answers to a TMS safety-screening questionnaire. Our study was approved by the Ethical Committee of Istanbul Medipol University (Ethical Report: 10840098–604.01.01-E.45425). All patients and their relatives gave written informed consent, and all protocols were applied in Istanbul Medipol University Hospital. Patients were examined during routine therapy where the medical treatment was not modified during the study period.

2.2. Experimental design

Each patient received 10 sessions of rTMS therapy for two weeks. One week prior to TMS the following data was collected from patients: expanded Turkish version neuropsychometric tests, fMRI, and blood serum. After the two weeks from TMS therapy, the same data were recollected from patients (Fig. 1).

2.3. Identification of stimulation locations and rTMS parameters

We determined a stimulation coordinate for each patient using individual maps of hippocampal resting-state functional connectivity collected before the TMS therapy. For each patient, we placed a seed (3 mm^3) to MNI coordinates $x = -24$, $y = -18$, $z = -18$, and voxel coordinates 57, 54, 23 (Wang et al., 2014), so that we found a localization in the cortex that was higher functional connectivity with the left hippocampal area. All coordinates we found corresponded to the left lateral parietal cortex, Brodmann area 7 (Fig. 2, Table 1). After that, we applied

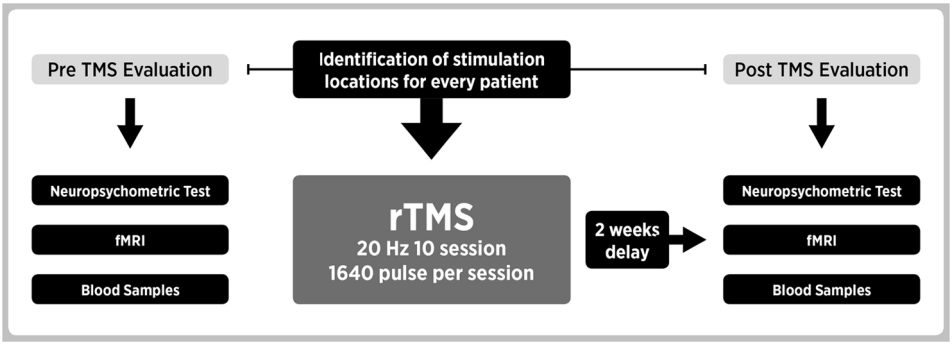

Fig. 1. Experimental design: The evaluation of neuropscyhometric test scores, fMRI parameters, and blood samples before and after the rTMS application of 20 Hz 10 session (1640 pulse per session).

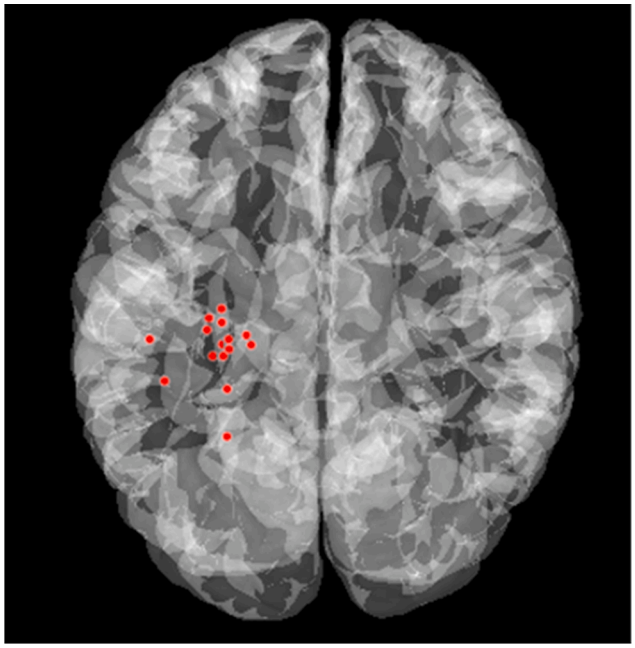

Fig. 2. The site of stimulated localisations depicted for every participant as red points (prepared from http://visbrain.org/auto_examples/index.html).

Table 1
The mean value of the stimulated coordinates for every participant according to MNI.

Patient Number	MNI Coordinate		
	x	y	z
s1	−24	−46	64
s2	−22	−62	57
S3	−22	−52	59
S4	−24	−44	66
s5	−22	−51	63
s6	−35	−60	56
s7	−28	−46	57
s8	−23	−56	64
s9	−17	−54	73
s10	−16	−54	67
s11	−22	−71	47
s12	−24	−49	55
s13	−26	−54	59
s14	−28	−41	53
s15	−43	−47	52
Mean	−25.0	−52.4	59.4

rTMS to these coordinates through the instrument of the "Brainvoyager TMS Neuronavigation" system. To get 3-dimensional brain imaging by means of Power "Mag for CMS20" software, we used the T1 weighted MR image of each patient in the neuronavigation system. Spatial position communication between the TMS coil and the patient's head (brain) was transferred to the neuronavigation software via small apparatus emitting sound waves.

We used the PowerMag Research tool of the Mag&More company for the TMS application. The coil type of TMS device was an "eight" coil, and the winding diameter of the coil was 2x70 mm. At the beginning of the first study week, we determined the motor threshold by stimulating the TMS primary motor area which required at least 5 of 10 consecutive pulses that must generate contraction in the *abductor pollicis brevis* muscle. TMS coil orientation was by handle pointing 45° to the midsagittal line held over the left parietal cortex, which generates a posterior to anterior current (Brown, Boyd, Ledwell, & Neva, 2014). The coil was approached manually to the coordinate shown in the neuronavigation system. We applied rTMS at 100% motor threshold during the 20 min on stimulation locations. rTMS protocol was 20 Hz for two seconds stimulation time (per session at totally 1640 pulses), followed by 28 s of interstimulus interval (no stimulation) (Nilakantan et al., 2017; 2019;; Wang et al., 2014; Wang & Voss, 2015).

2.4. Neuropsychometric tests

For global cognitive assessment, we used the Mini-Mental State Examination (MMSE) (Güngen, Ertan, Eker, Yaşar, & Engin, 2002). Attention functions were evaluated due to the Digit Span Test (Bosgelmez et al., 2015). Wechsler Memory Scale (WMS) was used as part of a general neuropsychological evaluation. Memory functions were evaluated WMS Logical Memory (Immediate and Delayed), WMS Visual Reproduction Test (Immediate and Delayed), WMS Visual Reproduction Test Recognition (Karakas et al., 1996), and Oktem Verbal Memory Process Test (Turkish Verbal Memory Test: SBST) (Oktem, 1992); language skills were tested by Boston Naming Test (Ekinci-Soylu & Cangöz, 2018); visual and perceptual functions were measured by Judgement of the Line Orientation Test (Spencer et al., 2013) and Benton Facial Recognition Test (Schretlen, Pearlson, Anthony, & Yates, 2001); and executive functions were evaluated by abstraction, the Semantic Fluency, the Stroop Test (Karakas et al., 1999), and the Clock Drawing Test. Patients were evaluated for nonmotor and behavioral symptoms with the Geriatric Depression Scale (GDS) (Ertan et al., 1997) and The Neuropsychiatric Inventory Questionnaire (NPI) (Akca-Kalem, Hanagasi, Cummings, & Gurvit, 2005), while the dementia level was determined with the Clinical Dementia Ratio (CDR) (Morris, 1993). All neuropsycometric tests were scored before and after TMS by the same qualified neuropsychologist who was also blind to the study hypothesis.

2.5. fMRI procedure and analysis

fMRI of the patients was performed with the Philips Achieva 3 Tesla (Philips Medical Systems, Best, Holland). The resting-state activity was recorded for functional imaging after the patient was positioned in the MR device, and the calibration was completed. In order to get a well-resting image, patients were asked to keep their eyes open and to stand without a move. fMRI recording lasted approximately 12 min and 300 volumes were displayed (TR 2230 ms, TE 30 ms, FA 77°) (TR/TE: 2230/30 ms), FOV 240x240x140 mm (RLxAPxFH), voxel size 3x3x4 mm, flip angle 77°, and slices 35. The recording parameters for the anatomical T1 image of the sagittal section were 190 slices; (TR/TE: 8.1/3.7), FOV 256x256x190 mm (FHxAPxRL), voxel size was determined as 1x1x1 mm.

For the fMRI analysis, we used the FMRIB FSL software tools on the Linux Mint 18.3 Sylvia operating system (ver.5.0.10, https://www.fmrib.ox.ac.uk/fsl). The raw data obtained from the MR device as DICOM single slice images were converted to NIFTI format with dcm2niix (ver. V1.0.20170724) command-line tool for the subsequent processing steps. The FSL fsl_anat script was used for brain extraction. The preprocessing steps with the FSL FEAT tool were performed collectively for all subjects by choosing first-level analysis. In the pre-processing stages, functional images were aligned to the center image, and motion correction was applied. A high pass filter cutoff was applied with a time constant of 150 s, which is well below the 0.01–0.1 Hz range where the resting state networks are observed, and the smoothing kernel FWHM was determined as 6 mm. The main structural image was used for each subject "higress.nii.gz" brain extracted image that was gained from the fsl_anat tool. The main structural image was linear (regular search, 12 DOF), and standard space was nonlinear (warp resolution: 10 mm). Independent component analysis was performed with the FSL MELODIC ICA tool. In order to clean functional data from the artifacts, due to general body/head movement, respiratory and cardiovascular origin, and device-dependent slow signal fluctuations, ICA components depending on their time course, frequency content, and spatial distribution manually labeled. The ICA components labeled as artifacts are removed from the functional data by using the FS fsl regflit tool. Following the preprocessing step cleaned functional data anatomical images of individuals were registered to the MNI152 standard brain using the FSL apply warp tool. Group level ICA was run on the standard brain images to obtain ICA components. The individual time series and spatial maps of ICA components were calculated by applying two-stage regression with the FSL dual regression tool. The distribution of the data was calculated by the permutation method (5000 times). The data from the two groups were compared with the Single-Group Paired Difference (Paired T-Test). For that analysis, we set up a glm matrix by using a pattern from the GLM-FslWiki website. Corrected p-values were calculated for multiple comparisons; $p < 0.05$ was considered significant. In addition to a comparison of group-level ICA components, a region of interest (ROI) analyses were performed with makes defining thalamus, globus pallidus, and amygdala, insula, cingulate cortex, right-left superior frontal regions. The final stage of the analysis was repeated with these ROIs, and group-level differences were compared for each ROI.

2.6. Blood serum analysis

Blood samples were collected from all patients before and after two weeks of TMS therapy. Then these blood samples were put into the gel biochemistry tubes and centrifuged at 3.500 g for 10 min at room temperature and were stored at −80 °C until the study was completed.

2.7. Determination of BDNF levels

BDNF levels were measured by the ELISA method using a commercial human BDNF ELISA kit (Catalog number: E-EL-H0010, Uniprot: P23560, Elabscience). BDNF content was expressed as equivalent to human recombinant BDNF protein (ng of BDNF protein/ml of serum). All steps of the analysis have been implemented according to the criteria designed by the manufacturer of the Elabscience on the website (https://www.elabscience.com/p-human_bdnf(brain_derived_neurotrophic_factor)_elisa_kit-17876.html).

2.8. Determination of serum total oxidant status

Total Oxidant Status levels were measured with Erel's method in serum samples (Erel, 2005). Calibration of the assay performed with H_2O_2 and results was expressed as H_2O_2 equivalent per liter (μmol H_2O_2 equiv/L). The precision values of this assay were 2%.

2.9. Determination of serum total antioxidant status

A fully automated Total Antioxidant Status assay was used according to Erel's method (Erel, 2004). Antioxidants suppressed these oxidative reactions and prevent color formation. The reaction was performed using spectrophotometry at 240 nm with an automated analyzer (Varioskan Flash Multimode Reader; Thermo Fisher Scientific, Waltham, MA, USA). Trolox was used as a calibrator. In the present study, the results are expressed as millimoles of Trolox equivalent per liter millimole (mmol Trolox eq/L). The precision of the assay was 3%.

2.10. Oxidative stress index

The degree of Oxidative Stress Index was basically, sophisticated ratios of serum Total Oxidant Status and Total Antioxidant Status levels and expressed as a percentage of serum Total Oxidant Status and Total Antioxidant Status levels. The used formula was this calculation is:

$$\text{Oxidative Stress Index (arbitrary unit)} = \frac{(\text{Total Oxidant Status, } \mu\text{mol H2O2 eq/L})}{(\text{Total Antioxidant Status, } \mu\text{mol Trolox eq/L})}$$

2.11. Determination of thiol/disulfide homeostasis

Novel oxidative stress biomarkers are serum native thiol and disulfide. A spectrophotometric determination was performed (Varioskan Flash Multimode Reader, Thermo, Waltham, MA), as described by Erel and Neselioglu (Erel & Neselioglu, 2014). Disulfide/native thiol ratio (-S-S-/-SH) was calculated as dynamic thiol-disulfide homeostasis.

2.12. Statistical analysis

Due to the fact that some of the neuropsychometric and blood serum data are not normally distributed (Shapiro-Wilk test), we used the Wilcoxon signed-rank test by Jamovi (ver. 1.2.22) software for the pre and post-treatment evaluation of the whole group. Kendall's Tau-B analysis was used to make correlative evaluations between data. In the fMRI analysis, the paired t-test was applied on the FSL software, which calculated a single group-matched difference by using the GLM matrix.

3. Results

3.1. Clinical and demographic data

The mean age of the patients was 69.86 ± 8.23, years. All patients had mild to severe AD symptoms (CDR ≥ 1). The mean cognitive scores and demographic features of the patients are shown in Table 2.

3.2. Power analysis

We have found that at least the sample size of n = 13 subjects are required for 90% power with a significance level of α = 0.05 which led

Table 2
Baseline demographic characteristics of the patients.

Characteristic	
N	15
Age	69.86 ± 8.23
Sex (male/female)	5/10
MMSE score (pre treatment)	18.09 ± 4.74
Handedness (left/right)	1/14

us to include at least n = 15 subjects in the study.

3.3. Assessment of cognitive scores after rTMS application in lateral parietal cortex

rTMS stimulation on the left lateral parietal cortex indicated a statistically significant improvement in WMS-Visual Reproduction Test Recognition scores (pre TMS mean = 1.4 SE = 0.32; post TMS mean = 2.33 SE = 0.36p = 0.017) and a nearly significant increase Clock Drawing scores (p = 0.054) after two weeks of the last stimulation session (Table 3) while other cognitive scores were not changed statistically significant (Table 3, $p > 0.05$).

3.4. fMRI data

3.4.1. Whole-brain analysis

A significant decrease in resting-state activity was observed in the occipito-fusiform gyrus as compared to before the rTMS intervention (Fig. 3a-3b, Table 4, $p < 0.05$).

3.4.2. Roi analysis

In determining the fusiform gyrus (Fig. 3a-3b, Table 4, $p < 0.05$), and lateral occipital cortex as seed ROIs, we have found a significant decrease in resting-state activity in the precuneus (Fig. 4a, Table 4, $p < 0.05$) as compared to before the rTMS intervention. Furthermore, we have observed a significant increase in resting-state activity in the frontal opercular cortex (Fig. 4b, Table 4, $p < 0.05$) as compared to before the rTMS intervention.

3.5. Blood levels of BDNF, oxidative injury markers, and antioxidant status

BDNF (Table 5, pre TMS mean = 372.01, SE = 42.41; post TMS mean = 508.61, SE = 47.55, p = 0.012), Total Antioxidant Status (Table 5, pre TMS mean = 0.69, SE = 0.03; post TMS mean = 0.86, SE = 0.04; p = 0.001), Total Thiol (Table 5, pre TMS mean = 353.44, SE = 9.97; post TMS mean = 388.88, SE = 12.14; p = 0.008), Native Thiol (Table 5, pre TMS mean = 233.47, SE = 7.85; post TMS mean = 293.38, SE = 10.77p < 0.001) levels were significantly increased as compared to before the rTMS treatment. Accordingly, Total Oxidant Status (Table 5, pre TMS mean = 14.45 SE = 0.45; post TMS mean = 12.13, SE = 0.37; $p < 0.001$), Oxidative Stress Index (Table 5, pre TMS mean = 22.07, SE = 1.77; post TMS mean = 14.99, SE = 1.61; p = 0.001) and Disulphide (Table 5, pre TMS mean = 59.98, SE = 4.33; post TMS mean = 47.74, SE = 3.59; $p <$ 0.001) levels were significantly decreased as compared to before rTMS treatment.

3.6. Correlation analysis

Kendall's Tau-beta correlation analysis revealed a significant positive correlation among the Clock Drawing – WMS-Visual Reproduction Test Recognition (Table 6, p = 0.046, τ = 0.462), Total Thiol – Total Antioxidant Status (Table 6, p = 0.016, τ = 0.467), while there was a negative correlation among the Total Oxidant Status – BDNF (Table 6, p = 0.027, τ = -0.429).

4. Discussion

In our study, we have found a statistically significant increase in visual recognition memory functions (p = 0.017) and a nearly significant increase in clock drawing test scores (p = 0.054) which were associated

Table 3
Neuropsychometric tests results.

Neuropsychometric Test	Pre TMS					Post TMS					Wilcoxon-Rank Test		
	N	M	Mdn	SD	SE	N	M	Mdn	SD	SE	Statistic	p	*Cohen's d*
Global Cognition													
MMSE	11	18.09	17	4.74	1.43	11	17.90	18	3.7	1.11	26.5	0.959	−0.036
Attention													
Digit Span Forward	15	4.86	5	1.12	0.29	15	4.73	5	1.1	0.28	45.5	0.594	0.1667
Digit Span Backward	15	2.86	3	1.12	0.29	15	2.8	3	1.20	0.31	20.0	0.829	0.1111
Executive Functions													
Semantic Fluency Fruit-Name	13	4.38	3	3.17	0.88	13	3.76	4	2.58	0.71	46.5	0.244	0.4091
Semantic Fluency Animal	14	12.35	9.5	7.51	2.00	14	11.71	10.5	8.02	2.14	48.5	0.861	0.0659
Phonemic Fluency KAS	14	20.57	18.5	15.73	4.20	14	22.35	19	18.46	4.93	19.0	0.23	−0.424
Stroop Test Duration Difference	8	71.75	67.5	31.28	11.05	8	66.75	64.5	24.2	8.55	19.0	0.945	0.0556
Clock Drawing	15	2	2	1.64	0.42	15	2.73	3	1.43	0.37	0.00	0.054	−1
Memory													
WMS-Visual Reproduction Test Immediate Recall	15	3.86	3	3.54	0.91	15	3.66	3	4.06	1.05	37.0	0.754	0.1212
WMS-Visual Reproduction Test Delayed Recall	15	0.4	0	0.91	0.23	15	0.53	0	1.12	0.29	2.0	0.773	−0.333
WMS-Visual Reproduction Test Recognition	15	1.4	1	1.24	0.32	15	2.33	2	1.39	0.36	9.0	**0.017**	−0.769
SBST Total Learning	14	46.28	46	18.41	4.92	14	49	45	18.86	5.04	42.0	0.53	−0.2
SBST Delayed Recall	14	1.07	0	1.73	0.46	14	1.07	0	1.54	0.41	12.0	0.796	−0.143
SBST Recognition	14	8.07	8	4.28	1.14	14	8	8.5	3.37	0.90	46.0	1	0.011
Language Skills													
Boston Naming Test Spontaneous	15	20.66	21	5.97	1.542	15	20.26	22	6.85	1.76	54.0	0.568	0.1868
Visual and Perceptual Functions													
Benton Facial Recognition	15	40	39	3.20	0.82	15	39.4	41	6.44	1.66	61.0	0.614	0.1619
Judgement of Line Orientation	9	18	18	6.70	2.23	9	16.88	19	7.84	2.61	22.0	0.622	0.2222
Behavioral													
Geriatric Depression Scale	13	9.61	7	7.26	2.01	13	9.53	7	6.51	1.80	39.0	1	0
Neuropsychiatric Inventory Questionnaire	12	11.75	10	13.29	3.83	12	9.5	8.5	9.71	2.80	42.0	0.448	0.2727

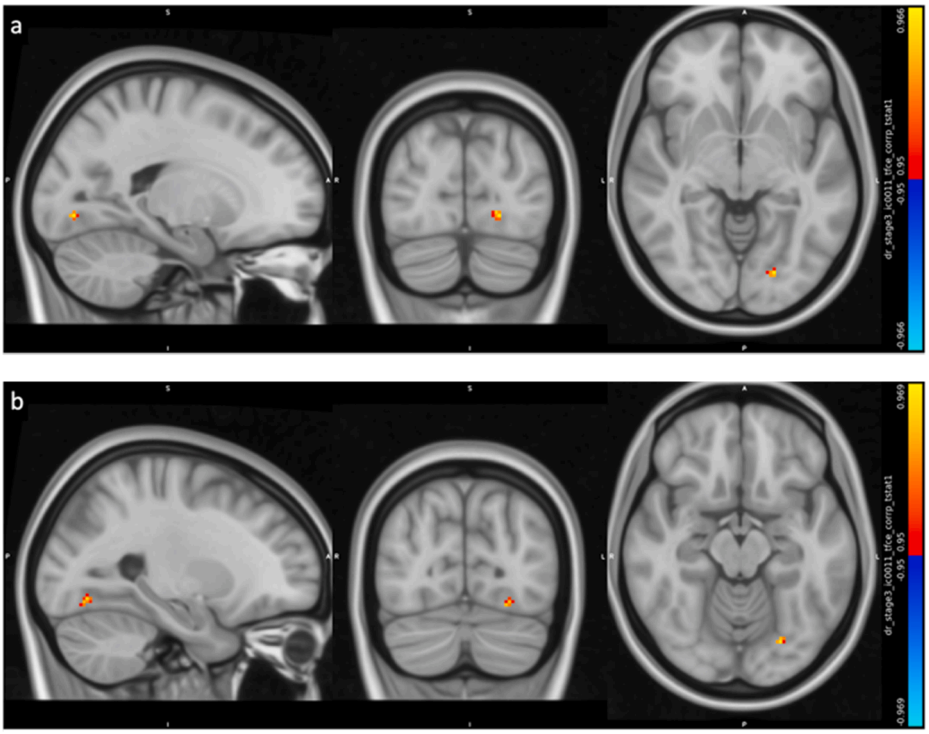

Fig. 3. There was an increased baseline activity in the occipito-fusiform gyrus (before the rTMS) which is improved after the rTMS application (Fig. 3a-3b).

Table 4
Clusters of fMRI activity.

Activity Area	Cluster Index	Voxels	1-p-MAX	1-p-MAXX (vox)	1-p-MAX Y (vox)	1-p-MAX Z (vox)	1-p-COGX (vox)	1-p-COG Y (vox)	1-p-COG Z (vox)	COPE-MAX	COPE-MAXX (vox)	COPE-MAX Y (vox)	COPE-MAX Z (vox)	COPE-MEAN
Occipital Fusiform Gyrus	1	13	0.966	55	23	33	54.2	22.8	33.1	7.16	55	23	33	6.15
	2	18	0.969	57	25	29	57.5	26.3	30	7.45	57	25	29	6.07
Precuneus Cortex	1	224	0.972	43	28	60	43.7	29.3	58.3	5.95	43	28	60	4.67
Central Opercular Cortex	1	17	0.981	22	68	38	22.1	67.1	39	9	22	68	38	7

with elevated peripheral BDNF levels, increased antioxidant capacity, and decreased oxidant enzyme activity after two weeks of left lateral parietal TMS stimulation (Fig. 5). In addition to the crucial role of the parietal cortex in encoding and retrieval of associative memories (Davidson et al., 2008), several cognitive neuroscience studies have shown that in particular the left lateral parietal cortex is specifically involved in the modulation of recollection and familiarity-based memory processes which are essential components of recognition memory (McDermott et al., 2009; Nelson et al., 2010; Simons et al., 2008). Herein, although recollection and familiarity represent two processes involved in general episodic memory retrieval, a number of cognition studies have suggested that recollection and familiarity are independent (separate) and functionally distinct processes reflecting different levels (degrees) of memory load (Merkow, Burke, & Kahana, 2015; Medina, 2008). However, only a few fundamental studies on the mechanisms underlying distinct retrieval processes have been reported. Hereby several studies evaluating the differences between recollection and familiarity based memory processes (Wang & Yonelinas, 2012; Yonelinas, 2002) have suggested that recollection includes retrieval of contextual details while familiarity links to an implicit-memory process based on prior experience (Park & Donaldson, 2016), which does not require mental reinstatement as has been proposed for recollection (Groussard et al., 2010).

Based on the key role of the left parietal cortex in the recollection and familiarity processes we expected to observe an increase in the recollection and familiarity components of the recognition memory. A surprising observation in this study which has not been previously demonstrated was that recollection and familiarity processes were not equally affected. Interestingly, although we have observed significant improvement in the Visual Reproduction Recognition Subtest of Wechsler Memory Scale (Williams et al., 1998) scores ($p = 0.017$) we have found no significant improvements in the WMS-Visual Reproduction Test Immediate Recall or WMS-Visual Reproduction Test Delayed Recall scores. The rationale behind our prediction was that the Visual Reproduction Subtest of Wechsler Memory Scale scores depends on familiarity with the items and clues evident in the subtest when compared to immediate visual memory or delayed recall memory scores which correspond to a rather contextual detail.

Several rTMS studies have shown that rTMS may improve the implicit memory functions (Grafman & Wassermann, 1998; Taylor & Thut, 2012; van de Ven & Sack, 2013). Also, implicit memory-priming mechanisms (Schacter, Bowers, & Booker, 1989) have already been reported to be involved in visual memory processing (Tulving et al., 1982). Together with these reports, our results showing improved visual

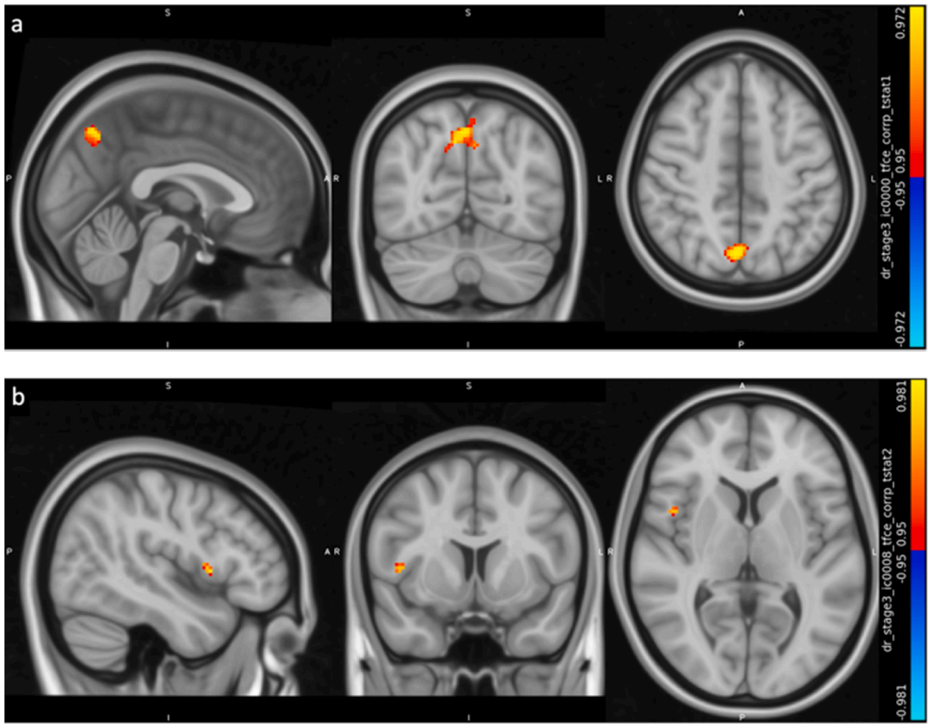

Fig. 4. Seed-based correlation analysis showed that there was an increased baseline activity in the precuneus cortex (before the rTMS) which was improved after the rTMS application (Fig. 4a). Additional seed-based correlation analysis showed that there was a decreased baseline activity in the right opercular frontal cortex (before the rTMS) which was improved after the rTMS application (Fig. 4b).

Table 5
Blood sample test results.

Blood Test	Pre TMS					Post TMS					Wilcoxon-Rank Test		
	N	M	Mdn	SD	SE	N	M	Mdn	SD	SE	Statistic	*p*	*Cohen's d*
BDNF	15	372.01	377.06	164.26	42.41	15	508.61	570.14	184.17	47.55	17	0.012	−0.717
Total Oxidant Status	15	14.45	14.59	1.75	0.45	15	12.13	11.98	1.44	0.37	114	< 0.001	0.9
Total Antioxidant Status	15	0.69	0.76	0.14	0.03	15	0.86	0.9	0.16	0.04	7	0.001	−0.883
Oxidative Stress Index	15	22.07	19.95	6.85	1.77	15	14.99	13.45	6.24	1.61	113	0.001	0.883
Total Thiol	15	353.44	358.11	38.62	9.97	15	388.88	411.68	47.03	12.14	15	0.008	−0.75
Native Thiol	15	233.47	219.32	30.42	7.85	15	293.38	286.33	41.71	10.77	3	< 0.001	−0.95
Disulphide	15	59.98	58.363	16.80	4.33	15	47.74	45.30	13.92	3.59	115	< 0.001	0.917

memory recognition scores suggest that rTMS might improve familiarity-based memory functions. Additionally, recent studies investigating the neuroimaging correlates underlying the pro-cognitive effects of rTMS in healthy subjects demonstrated a significant association between improved memory scores (associative and visual recollection) and regional and network alterations in precuneus, fusiform gyrus, left parietal cortex, and hippocampus (Nilakantan et al., 2017; 2019;; Wang et al., 2014; Wang & Voss, 2015). These study results were confirmed by other fMRI studies showing increased activity in the retrosplenial cortex, fusiform gyrus, lateral parietal cortex, and superior parietal cortex after the rTMS application (Freedberg et al., 2019).

However, even though there are several reports on the pro-cognitive effects of rTMS, these studies have not sufficiently discussed the role of the familiarity-based recognition process. For instance, it is noteworthy that these studies have characterized and discussed memory recognition as a part of the recollection process rather than as a familiarity-based recognition. Another significant difference between our findings and previous authors is that we have found decreased activity in the precuneus and fusiform gyrus whereas previous studies have reported increased activity in the precuneus and fusiform gyrus. Besides, we have found that familiarity-based test scores (especially the Visual Reproduction Test Recognition) were significantly increased after the rTMS application indicating an improved implicit memory process. It is difficult to explain this discrepancy between our results and other study findings (Freedberg et al., 2019; Nilakantan et al., 2017; 2019;; Wang et al., 2014; Wang & Voss, 2015); however, one possible explanation could be that our study samples are not entirely comparable to other studies due to a higher mean age and disease condition, while the patients in other studies were healthy and relatively younger. Hence, to the best of our knowledge, there are no previous studies on the therapeutic correlates of rTMS in AD patients to compare our findings. Nevertheless, despite the above inconsistencies, we believe that our fMRI findings fit well with recent neuroimaging data in AD patients showing increased activity in similar brain regions. For instance, previous clinical studies comparing patients with MCI, SCI, and AD to healthy controls have shown that the hippocampus, fusiform gyrus, precuneus, and lingual gyrus were among the most activated regions in these patients (Cai et al., 2015; He et al., 2007; Li et al., 2018; Schwindt & Black, 2009). Considering all of these points, our favored interpretation is that rTMS normalizes the overactivity of brain regions associated with the degenerative process of AD.

Our Clock Drawing Test results did not reach statistical significance ($p = 0.054$), hypothesized to relate with alteration of the fusiform gyrus, precuneus, and right frontal opercular area activity. Nevertheless, our

Table 6
Kendall's Tau-beta correlation results.

Correlation Matrix		Clock Drawing	WMS- Visual Reproduction Test Recognition	BDNF	Total Oxidant Status	Total Antioxidant Status	Oxidative Stress Index	Total Thiol	Native Thiol	Disulphide
Clock Drawing	Kendall's Tau B	—								
	p	—								
WMS- Visual Reproduction Test Recognition	Kendall's Tau B	0.462	—							
	p	**0.046**	—							
BDNF	Kendall's Tau B	−0.065	0.17	—						
	p	0.765	0.408	—						
Total Oxidant Status	Kendall's Tau B	−0.375	−0.383	−0.429	—					
	p	0.083	0.062	**0.027**	—					
Total Antioxidant Status	Kendall's Tau B	0.271	0.277	0.2	—	—				
	p	0.209	0.178	0.328	—	—				
Oxidative Stress Index	Kendall's Tau B	−0.22	−0.319	−0.314	—	—	—			
	p	0.309	0.121	0.114	—	—	—			
Total Thiol	Kendall's Tau B	0.194	0.192	0.352	−0.276	0.467	−0.314	—		
	p	0.37	0.352	0.074	0.169	**0.016**	0.114	—		
Native Thiol	Kendall's Tau B	0.116	0.213	0.257	−0.295	0.257	−0.219	—	—	
	p	0.59	0.301	0.202	0.139	0.202	0.282	—	—	
Disulphide	Kendall's Tau B	0.09	−0.064	−0.067	0.067	0.2	0.029	0.352	0.029	—
	p	0.676	0.756	0.77	0.77	0.328	0.923	0.074	0.923	—

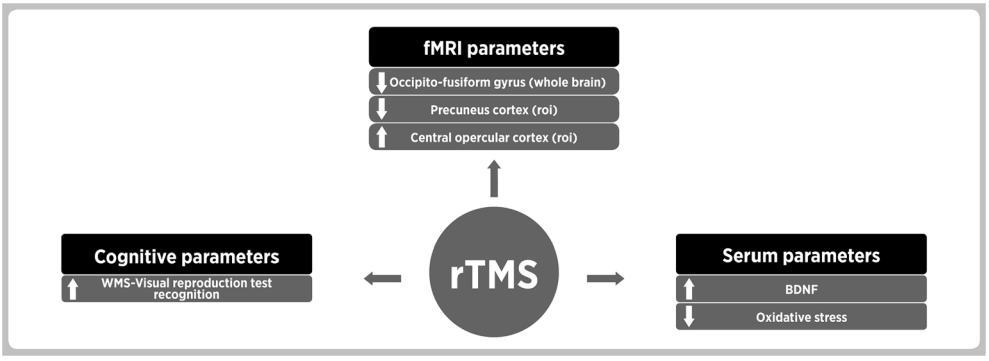

Fig. 5. Main effects of rTMS on fMRI, serum, and cognitive parameters showing decreased oxidative stress parameters, increased BDNF levels, and altered resting-state fMRI activity in AD patients.

findings showing a significant alteration in clock drawing specific brain regions (decreased fusiform gyrus, precuneus, and increased right frontal opercular area activity), are generally in line with previous studies showing significant functional differences between normal individuals and AD patients (Kang et al., 2019; Leyhe et al., 2009; Talwar et al., 2019). With this, several structural, metabolic and functional neuroimaging studies have suggested that impaired Clock Drawing Test performance scores are associated with altered activity of frontal and parietal regions in dementia (Brugnolo et al., 2010; Kim et al., 2009; Shon et al., 2013). Conversely, fusiform, and right frontal (opercular) Blood Oxygen Level Dependent (BOLD) activity has been recently reported to be decreased during the Clock Drawing Test in healthy individuals (Talwar et al., 2019). Beyond indicating that rTMS has a modulatory effect on specific brain regions which is dysregulated in AD, we have provided additional evidence that BDNF and oxidative stress parameters (Kapczinski et al., 2008; Wei et al., 2020; Zhang et al., 2015) could be ideal biomarkers for rTMS. Herein we have shown that rTMS led to significant changes in BDNF levels, oxidative injury markers, and anti-oxidative stress parameters. From this point of view, our findings are in line with previous preclinical and clinical observations showing the pro-cognitive, antidepressant, and neuroprotective role of BDNF (Bathina & Das, 2015; Bramham & Messaoudi, 2005; Mattson, Maudsley, & Martin, 2004; Mora et al., 2019; Peng, Wuu, Mufson, & Fahnestock, 2005). Additionally, our findings showing a significant inverse relationship between oxidative stress parameters and BDNF levels is consistent with previous studies showing a significant association between oxidative injury and the progress of neurodegenerative diseases (Butterfield & Halliwell, 2019; Schrag et al., 2013; Taylor & Crack, 2004). Moreover, the role of rTMS on BDNF levels reported in our study might provide further rationale for exploring the therapeutic correlates of rTMS (Ma et al., 2014; Makowiecki, Harvey, Sherrard, & Rodger, 2014; Niimi et al., 2016; Zhao, Li, Cong, Zhang, & Tan, 2017). Here, it is noteworthy to mention that changes of candidate biomarkers reported in our study might help in the future in adopting a more tailored approach to treat AD patients with rTMS.

5. Limitations

Although our study may provide important information about the probable disease-modifying efficacy of the rTMS, several limitations of our study must be also considered. First, despite the valuable information gained in our study, the results of this pilot study should be considered preliminary due to the lack of a control group. Second, our sample size was small and we have examined only the short-term effect of rTMS. Third, since serum BDNF levels contain a much lower proportion of BDNF originating in the central nervous system relative to plasma (Chacón-Fernández et al., 2016; Fernandes et al., 2015; Fujimura et al., 2002; Rasmussen et al., 2009) which requires large sample sizes for accurately interpreting the blood BDNF and oxidative stress levels, we have applied the power analysis only for the psychometric tests which can be considered as a minor limitation. Further, it is also notable that plasma and serum BDNF levels are not correlated and likely are biologically relevant to different functions (Gejl et al., 2019). Considering all of these limitations, replication of our results by multiple large cohorts of patients with appropriate control groups would be required before clinical recommendations could be made. In this respect, it could be interesting in future studies to investigate the long-term effects of the rTMS treatment on implicit memory in AD patients. As a conclusion, our study, though preliminary, has a potentially important clinical implication, suggesting that biomarker and neuroimaging evaluations could be added to target specific rTMS applications.

CRediT authorship contribution statement

Halil Aziz Velioglu: Conceptualization, Data curation, Writing - original draft, Investigation, Visualization. **Lutfu Hanoglu:** Resources, Methodology, Supervision, Project administration. **Zubeyir Bayraktaroglu:** Software, Supervision. **Guven Toprak:** Resources. **Eray Metin Guler:** Data curation. **Muhammed Yunus Bektay:** Formal analysis. **Ozlem Mutlu-Burnaz:** Data curation. **Burak Yulug:** Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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